JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review
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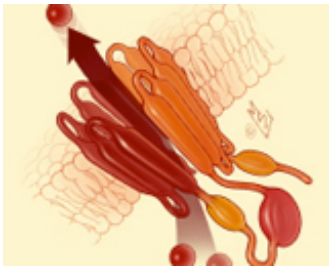

ecfs special edition

Special Edition: Highlights of the 35th European Cystic Fibrosis Conference

Welcome to Part 1 of this eCysticFibrosis Review Special Edition, our two-part series reporting on some of the key information presented at the European Cystic Fibrosis Society (ECFS) meeting in Dublin, Ireland June 6-9, 2012.

As an additional feature, many of these reports include links to streaming video of eCysticFibrosis Review Program Director Peter Mogayzel, MD discussing the new data with the presenters. Look for the  *to link to this feature.*

In this Issue...

Cystic fibrosis (CF) researchers and specialists from around the world came to Dublin, Ireland this past June to attend the 35th European Cystic Fibrosis Society Congress. They shared new findings about advances in CF lung infections, nutrition, and the use of *CFTR*-modifying therapies, and discussed the key gaps in the current knowledge that need to be better understood.

In this issue we report on presentations focusing on:

- **CF Lung Microbiology:** New longitudinal data reinforces the need for further research linking microbiota to clinical disease progression
- **Complex Infections:** New evidence marks *Achromobacter xylosoxidans* as a rapidly emerging multi-resistant pathogen with high morbidity, and new tactics have been developed to manage methicillin-resistant *Staphylococcus aureus* (MRSA)
- **Exacerbations:** The need to develop a more scientific means of therapy selection—identifying which organisms to target with which antibiotics—becomes even more important as new data shows exacerbations damage the lungs more than previously thought
- **Targeting basic the defect in CF:** Reports from recently completed and on-going trials in both children and adults with the G551D-*CFTR* mutation show that treatment with the *CFTR* potentiating agent ivacaftor provides durable effects in lung function improvement, reduction in exacerbations, delay in exacerbation onset, weight gain, and improved nutritional outcomes.

Program Information
CME/CE Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME/CE Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity
Physicians
1 hour
Nurses
1 contact hour

Release Date
October 4, 2012

Expiration Date
October 3, 2014

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LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe current research that reinforces the need to link CF lung microbiology to clinical outcomes.
- Explain when to suspect A. *xylosoxidans* infection and the evidence basis for effectively treating it.
- Evaluate current management tactics for MRSA infections.
- Discuss new data that quantifies the damage pulmonary exacerbations cause to CF lungs.
- Describe the impact of ivacaftor on lung function, weight gain and BMI in children and adult patients with CF with G551D *CFTR* mutations.

IMPORTANT CME/CE INFORMATION

▼ Program Begins Below

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INTENDED AUDIENCE

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dieticians, nutritionists, nurses, and physical therapists.

LAUNCH DATE

This program launched on October 4, 2012, and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

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STATEMENT OF NEED
Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

- Very recent developments in strategies for treating P. aeruginosa, using existing as well as new antibiotics, are only beginning to penetrate the awareness of clinicians who should be familiar with the most effective means of treating this dangerous pathogen.
- CF clinicians lack adequate clinical guidance in managing pulmonary exacerbations.
- CF clinicians are not aware of and/or are not implementing existing strategies for improving patient adherence to antibiotic medications.

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General Counsel, Johns Hopkins Medicine (4/1/03)
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IN THIS ISSUE

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Unlabeled/Unapproved Uses

Drs. Mogayzel and Binder have indicated that there will be reference to the following unlabeled or unapproved uses of drugs: colistin, tobramycin.

Planning Committee Disclosures

NEW INSIGHTS INTO THE MICROBIOLOGY OF THE CF LUNG

Symposium 6: New Insights into the Microbiology of the CF Lung
The Molecular Microbiome of the Respiratory Tract. Kenneth Bruce, PhD. Talk from the 35th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland.

Chronic airway colonization of CF lungs is typically a complex mix of bacterial species. At the ECFS New Insights into the *Microbiology of the CF Lung* symposium, investigators shared new data about the relationship between the lung microbiota and clinical parameters.

"There is evidence that for many patients with CF, the microbiota communities of the lungs are relatively stable over time despite antibiotic challenge. Also, links between microbiota composition and clinical parameters are emerging. In the longer term, our aim is to identify the microbial drivers of lung disease progression, facilitating improvements in patient treatment, " said Kenneth Bruce MD, of Kings College London, London, England, one of the key speakers.

Studies linking microbiota to clinical data are few and far between. Findings from earlier trials indicated a progressive loss of species diversity in the lungs of older patients over time, as compared to younger patients with CF. More recently, it was shown in a decade-long study that diversity decreased significantly only in those patients with progressive disease; another investigation showed that *P. aeruginosa* is often the sole pathogen in end stage CF lungs. "These studies show the microbiota, in some form, are linked to one

or more clinical measure. It is important to see, however, that species change with the disease status," Dr. Bruce noted.

Further, the majority of studies to date have been based on cross-sectional analyses. Dr. Bruce feels that researchers can better link microbial data with disease progression by following individual patients over time. Such longitudinal studies would be valuable to pre-empt exacerbations, monitor the impact of antibiotics, and identify the drivers of CF disease progression.

Take home message: *Long-term studies linking microbiological communities are still developing, both conceptually and practically. A fuller understanding of the microbiota of the CF lung will allow investigators to develop models to test treatments and study mechanisms. However, physicians need to be aware that colonization changes over time, and be prepared to adjust their clinical priorities accordingly.*

Dr. Peter Mogayzel and Dr. Kenneth Bruce discuss the molecular microbiome of the respiratory tract.

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MANAGING COMPLEX INFECTIONS IN ADVANCED LUNG DISEASE

Symposium 17: Managing Complex Infections in Advanced Lung Disease
Achromobacter; Marianne Skov MD. Talk from the 35th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland.

POSTER 353:
Achromobacter xylosoxidans in cystic fibrosis (CF): indirect patient-to-patient contact can lead to cross-infection; C. Rønne Hansen, T. Pressler, H.K. Johansen, M. Skov

POSTER 63:
Achromobacter xylosoxidans: Time to Recurrence and Antimicrobial Susceptibility; M. Wang, W. Ridderberg, C.R. Hansen, N. Høiby, et al Posters from the 35th ECFS Congress; June 6-9, 2012; Dublin, Ireland.

Achromobacter xylosoxidans is a rapidly emerging pathogen of increasing importance to clinicians. It causes serious, rapid, and early deterioration of lung function, is often multi-resistant (even when first isolated), and can easily cross infect. The 2010 Cystic Fibrosis Foundation annual report noted the prevalence of A. *xylosoxidans* at 6.2% and investigators believe this prevalence is quickly rising.

Marianne Skov MD, Rigshospitalet, Department of Pediatrics, Copenhagen, Denmark, shared her experience with this dangerous new pathogen during a symposium entitled: *Managing Complex Infections in Advanced Lung Disease*. "Patients with A. *xylosoxidans* often experience a rapid decline in lung function within a year of diagnosis, and if not aggressively treated will either require a lung transplant or die," she reported

A. *xylosoxidans* infections are challenging to treat because the pathogen quickly becomes multi-resistant. Dr. Skov treats first-time A. *xylosoxidans* infections intensively for 3 weeks using inhaled colistin along with oral amoxicillin and clavulanate. In cases of re-growth, she re-treats with 2 weeks of IV antibiotics in combination with oral

trimethorprine/sulphamethoxazole.

Eight of her A. *xylosoxidans* infected patients share an identical strain of the pathogen, suggesting cross infection from a common source. Direct and indirect person-to-person cross infection underlies the importance of segregation, she said.

"This corroborates what a number of other studies have shown, that social contact can spread A. *xylosoxidans*, with common strains and clusters being identified. Avoidance of even indirect contact between patients with CF with and without chronic infection is extremely important," she noted.

Christine Ronne Hansen MD, Rigshospitalet, Department of Pediatrics, Copenhagen, Denmark, agreed that the best way to avoid the crippling effects of *A. xylosoxidans* is to isolate patients who have been diagnosed with the infection.

In her poster, *Achromobacter xylosoxidans in cystic fibrosis (CF): indirect patient-to-patient contact can lead to cross-infection*, Dr. Hansen reported on 2 case studies of young patients (6 and 13 years) who were infected with *A. xylosoxidans* via indirect cross-infections, without direct patient-to-patient contact. Pulse field gel electrophoresis (PFGE) testing of isolates indentified strains identical to patients with known *A. xylosoxidans* infections they had only peripherally encountered.

The infected patients both received long-term aggressive antibiotic treatment once A. xylosoxidans was discovered. In spite of the aggressive regimen, however, they both developed chronic infections, and had sinus surgery due to *A. xylosoxidans* identification in sinus secretions. The tendency of *A. xylosoxidans* to colonize the sinuses highlights the importance of including a sinus assessment when evaluating a CF patient with rapid clinical deterioration.

In her poster *Achromobacter xylosoxidans: Time to Recurrence and Antimicrobial Susceptibility*, Michala Wang MD of Skejby Hospital, Department of Clinical Microbiology, Aarhus, Denmark, showed that the median time to recurrence of patients treated with either piperacillin-tazobactam, meropenem or trimethoprim-sulfmethoxazole (n=21) for a minimum of 14 days after isolation of *A. xylosoxidans* was 13.5 months. By contrast, patients infected with A. xylosoxidans receiving another antibiotic or no treatment (n=26) experienced a median time of recurrence of 4 months.

Her presentation described 47 patients who experienced first-time detection of *A. xylosoxidans* at 2 Danish CF centers from 2000 to 2011. She calculated the median time to recurrence using Kaplan-Meier estimation and outlined the minimal inhibitory concentration (MIC) of 14 antibiotics against 34 first-time isolates of *A. xylosoxidans* (determined by Etest®) and susceptibility data (interpreted according to the European Committee on Antimicrobial Susceptibility Testing - EUCAST - guidelines).

According to EUCAST, 100% of A. *xylosoxidans* isolates were susceptible to piperacillin-tazobactam, 94% to meropenem, 73% to colistin, 62% to ceftazidime, and 9% to tobramycin.

Take home messages: *A. xylosoxidans infections are a serious threat to lung function and can occur at any point in the lifetime of a patient with CF, and may be acquired through indirect contact. As colonization of the sinuses is common, a sinus assessment should be performed when evaluating a patient with CF with rapid clinical deterioration. Proper antibiotic selection to treat primary A. xylosoxidans colonization may postpone the time to recurrence, and the establishment of a chronic infection.*

Dr. Peter Mogayzel and Dr. Marianne S. Muhlebach from the North Carolina Children's Airway Center at the University of North Carolina, Chapel Hill discuss managing methicillin-resistant Staphylococcus aureus.

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EXACERBATIONS IN CF: OPTIMIZING OUTCOMES

Symposium 30: Exacerbations in CF: Optimizing Outcomes
Management of Exacerbation, what works? Diana Bilton MD. Pathogenesis and Immunobiology. Andrew Bush MD. Talks from the 35th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland.

Treatment of pulmonary exacerbation in patients with CF aims to restore FEV_1 to baseline values and return the symptoms to pre-exacerbation levels. New data explains why this goal has been so hard to achieve.

"Evidence suggests that 20% of patients with CF fail to return to baseline after an exacerbation, in spite of treatment. To answer why this happens, maybe we have to take exacerbation risk factors into account, target those patients, and stratify the numbers for a different approach more beneficial to them," said Diana Bilton MD, of Royal Brompton Hospital, London, UK in her *Management of Exacerbation, what works?* presentation.

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Risk factors associated with failure to recover baseline FEV_1 include: female gender, low BMI, medical insurance (socioeconomic status), microbiological status (*B. cepacia, P. aeruginosa*), allergic bronchopulmonary aspergillosis (ABPA), time from baseline lung function, and greater fall in FEV_1.

In addition, although antibiotics are clearly beneficial (as evidenced by the improved survival rates of patients with CF into the 40-50 year range), physicians are not always sure which organisms they need to target, and how effective the chosen antibiotics may actually be. Further, in the absence of biomarkers, physicians are left with patient feedback as primary means of selecting/continuing treatment. Therapy duration tends to trend with improvements in lung function and sputum (weeks to months), and the optimal duration of treatment has yet to be stratified, Dr. Bilton noted.

"It is really important that we keep doing what we know works, while questioning what we can do better. What works right now are antibiotics, physiotherapy to enhance airway clearance, and monitoring the entire patient response, not just FEV_1. We also need to know more about biomarkers to better understand exacerbations. We seem to still be following the same protocol that we were taught 20 years ago and that can not be right," she observed.

Although physicians who treat patients with CF report tens of thousands of exacerbations every year, a well-defined definition of exacerbations is largely lacking. CF specialists believe that the best way to pre-empt exacerbations is to understand what they are, how they come about, and take steps to avoid them.

In his presentation Pathogenesis and Immunobiology, Andrew Bush MD, of the Imperial Royal College and Royal Brompton Hospital, London, UK, stated: "The word exacerbation is really a feeble one that implies a minor inconvenience. It is not minor, however, and can be very serious. Unfortunately, very little is known on the topic."

What is known is that exacerbations cause lung conditions to worsen, making a full recovery difficult. Some evidence points toward persistent inflammation (oxidative stress) as an important trigger of exacerbation, while other studies have shown that CF exacerbations are likely to be associated with lung tissue destruction.

While most practitioners are familiar with the long list of organisms and environmental conditions thought to trigger CF exacerbations — human (non-adherence), bacterial (existent, new, non-cultured), viral, fungal, environmental, et al — the broad generic nature of exacerbation triggers makes it difficult to get a better grasp of them. "We have to respond to exacerbations in a more focused way", Dr. Bush explained, "This includes paying attention to the individual patient to understand what brought about the change for the worse, such as medication or adherence. Furthermore, we need to develop biomarkers for different types of exacerbations to help us gain an understanding of just what exactly we are trying to treat, and devise specific therapies. We cannot manage all exacerbations in the same way."

Take-home message: *Pulmonary exacerbations, common to most patients with CF, appear to damage the lungs more than previously thought, with only 1 in 5 patients not recovering to FEV_1 baseline. Risk factors for incomplete recovery have been identified, as have many of the conditions that trigger exacerbations. However, a lack of reliable biomarkers leave clinicians with patient feedback as their primary means of validating antibiotic efficacy, reinforcing the need to individualize exacerbation treatment.*

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NEW THERAPIES TARGETING BASIC DEFECTS

Workshop 6: New Therapies Targeting Basic Defects

Abstract WS6.3: Measures of Nutritional Status in Two Phase 3 Trials of Ivacaftor in Subjects with Cystic Fibrosis who have the G551D Mutation. D. Borowitz, B. Ramsey, Q. Dong, K. Yen, J.S. Elborn

Abstract WS6.4: Long-term Safety and Efficacy of Ivacaftor in Subjects in Cystic Fibrosis who have the G551D-CFTR Mutation. Edward McKone, H. Li, K. Yen, J.C. Davies.

Abstract WS6.5: Ivacaftor in Subjects 6-11 Years of Age with Cystic Fibrosis and the G551D-CFTR Mutation. J.C. Davies, H. Li, K. Yen, R. Ahrens, on behalf of the VX08-770-103 Study Group

Abstracts from the 35th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland.

Abstracts discussing results from 3 of the Phase 3 trials of the *CFTR* potentiating agent ivacaftor were presented at an ECFC workshop in Dublin. The STRIVE and ENVISION randomized double blind placebo-controlled studies tested the effects of ivacaftor 150mg q12h for 48 weeks (plus prescribed therapies) in patients with at least one G551D *CFTR* mutation.

STRIVE enrolled 167 adolescent and adult patients with CF (≥12 years) with FEV_1 at screening of 40-90% predicted. 78 were randomized to placebo and 83 to ivacaftor. Of the original 167subjects, 68 placebo and 77 ivacaftor patients finished the 48 weeks.

In ENVISION, 52 patients between 6-11 years of age with FEV_1 at screening of 40-105% predicted were randomized to either placebo (n=26) or ivacaftor (n=26). Four placebo patients withdrew, and all of the remaining patients finished the 48-week trial.

Reporting on weight and BMI change, Drucy Borowitz MD, of the State University of New York at Buffalo, New York, USA noted: "There was a slow but steady weight gain in both the adult/adolescent and children groups receiving ivacaftor, as compared to placebo." The treatment difference in mean weight change in the STRIVE trial was 2.8kg (p<0.0001) at Week 24 and 2.7kg (p=0.0001) at Week 48. In ENVISION, the treatment difference in mean weight change was 1.9kg (p=0.0004) at Week 24 and 2.8kg (p=0.0002) at Week 48.

"There was an inexorable, slow weight gain in the ENVISION ivacaftor group, which exceeded the 50th percentile in weight-for-age z-scores between placebo and ivacaftor patients," Dr. Borowitz observed. At Week 48, the treatment difference in BMI was 0.9kg/m2 (p<0.0001) in STRIVE and 1.1kg/m2 (p=0.0003) in ENVISION.

The presentation by Jane Davies MD, Royal Brompton Hospital, London, UK, focused on changes in respiratory symptoms, pulmonary exacerbation risk, and weight gain vs. placebo in the ENVISION study.

"Compared to placebo, ivacaftor led to a substantial and statistically significant improvement in pulmonary function, *CFTR* activity, and weight gain in this group of relatively well children. The improvements in FEV_1 were comparable to those seen in the previous study of older children and adults (STRIVE), despite significantly milder disease in this group," Dr. Davies reported.

The mean baseline FEV_1 in the ENVISION group was 84.2%±18.1%. The mean absolute change from baseline in percent predicted FEV_1 at Week 24 was 12.5% points (P<0.0001) and at Week 48 10.0% points (p=0.0006).

Ivacaftor led to significant reduction in sweat chloride, a measure of improved *CFTR* activity, through Week 48 (treatment difference: -53.5mmole/L; p<0.0001). The safety profile showed consistency with ivacaftor in adolescents/adults, and no new safety concerns were identified. The most commonly reported adverse events were respiratory in nature and had comparable incidence to placebo.

"Since earlier treatment may offer the greatest potential for benefits, we are very pleased to observe in this study, conducted in a very young patient group, a substantial, sustained, highly significant improvement in FEV_1," Dr. Davies noted.

Edward McKone MD, of St Vincent's University Hospital, Dublin, Ireland described results from the PERSIST study, where 192 placebo and ivacaftor patients who completed the STRIVE/ENVISION trials all received ivacaftor (150mg q12h) for (thus far) an additional 48 weeks/24 weeks, respectively.

"In subjects who had received placebo in the earlier studies, FEV_1 improvements were of similar magnitude to those observed in the prior studies of ivacaftor recipients, showing a rapid improvement in lung function. Ivacaftor patients coming out of ENVISION and STRIVE have maintained their lung function during the PERSIST study so far," he reported.

PERSIST included 144 STRIVE patients (≥12 years, FEV_1 40-90% predicted) of which 67 had received placebo and 77 had received ivacaftor. 64/67 placebo patients and 74/77 ivacaftor patients completed the additional 48 weeks of treatment. Roll-overs from ENVISION (6-11 years, FEV_1 40-105% predicted) included 22 placebo patients and 26 ivacaftor patients; of these, 22/22 placebo and 25/26 ivacaftor patients finished 72 weeks of treatment, so far.

The mean absolute change from baseline in lung function after 96 weeks in placebo patients who rolled over from STRIVE was 9.5% increase in FEV_1 predicted. The effects benefits seen early on in the STRIVE trial in patients taking ivacaftor remained for the full 96 weeks.

"Ivacaftor treatment delayed the onset of exacerbations, and the reduction in the number of exacerbations per subject observed with ivacaftor treatment in adults/adolescents was sustained in PERSIST," Dr. McKone noted.

Exacerbations in STRIVE and ENVISION differed in their numbers and time patterns. In the STRIVE study, patients taking ivacaftor exhibited virtually no exacerbations for a span of several weeks toward the end of the 48 week study period, while exacerbations in children (ENVISION) were insignificant throughout the study. A large number of exacerbations were observed, however, when patients rolled over to PERSIST. Almost 10% of all exacerbations took place at the time of roll over. Compared to the overall number of exacerbations seen in the two groups (placebo: 83 in total; ivacaftor: 64 in total), the ivacaftor group still had a lower rate of exacerbation, Dr McKone said.

Mean absolute change in BMI was sustained in ivacaftor patients who rolled over from STRIVE and ENVISION, and, within 10 weeks, was matched by placebo patients who rolled over from both studies into PERSIST.

The overall safety profile observed for subjects receiving ivacaftor in PERSIST was consistent with the safety profile observed during ivacaftor treatment in the original studies, with no new clinically important safety concerns identified

Quality of life respiratory domain score (CFQ-R) was improved in the STRIVE study by a clinically significant 4 points, and has maintained in PERSIST thus far. CFQ-R in rolled-over placebo patients spiked once they received ivacaftor, which was maintained at 96 weeks.

"The effects appeared durable in terms of weight and lung function up to 96 weeks. Those who received placebo showed reproducible effects later in PERSIST, which is very important," Dr McKone observed.

Take home message: *Ivacaftor (150mg q12h) increased weight gain and BMI in both children and adolescent/adult cystic fibrosis patients with at least one G551D CFTR mutation, and led to a substantial and statistically significant improvement in pulmonary function and CFTR activity in children with significantly milder disease. In adult and adolescent patients, ivacaftor treatment delayed the onset and reduced the number of exacerbations as compared to placebo. These results proved durable for up to 96 weeks, with no clinically important safety concerns.*

Dr. Peter Mogayzel and Dr. Edward F. McKone discuss the long-term safety and efficacy of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR mutation.

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